Docket No.: C15043/174944

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :	)	
Harold M. Bates	)	Examiner: Not yet assigned
Serial No.: 10/777,543	)	Expected Art Unit: 1646
Filed: February 12, 2004	)	
For: DETECTION OF ASYMPTOMATIC CORONARY ARTERY DISEASE USING ATHEROGENIC PROTEINS AND ACUTE PHASE REACTANTS	)	

SEVENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Mail Stop Amendment
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant wishes to make of record the documents identified below (clean copies and a Form PTO-1449 listing them are enclosed). **Applicant believes that that no fee is required for this paper** (see last paragraph).

169. Griffin ME, McInerney D, Fraser A, Johnson AH, Collins PB, Owens D, Tomkin GH. "Autoantibodies to Oxidized Low Density Lipoprotein: the Relationship to Low Density Lipoprotein Fatty Acid Composition in Diabetes." *Diabetic Medicine* (1997), volume 14, pages 741-747.

170. Liu K, Cuddy TE, Pierce GN. "Oxidative status of lipoproteins in coronary disease patients." *American Heart Journal* (1992), volume 123, pages 285-290.

171. Palinski W, Horkko S, Miller E, Steinbrecher UP, Powell HC, Curtiss LK, Witztum JL. "Cloning of Monoclonal Autoantibodies to Epitopes of Oxidized Lipoproteins from Apolipoprotein E-deficient Mice." *Journal of Clinical Investigation* (1996), volume 98, pages 800-814.

172. Schier R, McCall A, Adams GP, Marshall KW, Merritt H, Yim M, Crawford RS, Weiner LM, Marks C, Marks JD. "Isolation of Picomolar Affinity Anti-c-erbB-2 Single-chain Fv by Molecular Evolution of the Complementary Determining Regions in the Center of the Antibody Binding Site." *Journal of Molecular Biology* (1996), volume 263, pages 551-567.

173. Winzor DJ, De Jersey J. "Biospecific Interactions: Their Quantitative Characterization And Use For Solute Purification." *Journal of Chromatography* (1989), volume 492, pages 377-430.

REMARKS

The relevance of each of these documents is set forth below.

169. Griffin ME, McInerney D, Fraser A, Johnson AH, Collins PB, Owens D, Tomkin GH, "Autoantibodies to Oxidized Low Density Lipoprotein: the Relationship to Low Density Lipoprotein Fatty Acid Composition in Diabetes," *Diabetic Medicine* (1997), volume 14, pages 741-747. "Autoantibodies to oxidized low density lipoprotein have been shown to be an independent predictor of the progression of carotid atherosclerosis. ... Antibodies to malondialdehyde-modified low density lipoprotein and copper-oxidized low density lipoprotein were determined by an ELISA method. Autoantibodies to copper-oxidized low density lipoprotein were significantly higher in the non-diabetic patients with heart disease when compared to any other group ($p < 0.05$). Autoantibodies to malondialdehyde-modified low density lipoprotein were significantly higher in the non-diabetic subjects with heart disease and in both diabetic groups compared to non-diabetic subjects without coronary heart disease ($p < 0.05$). ... This study confirms the association between antibodies to oxidized low density lipoprotein and coronary heart disease and shows raised low density lipoprotein antibody levels in

diabetic patients with and without demonstrable atherosclerosis." (Abstract) "The purpose of this study was to define the relationship between the LDL fatty acid composition, antibodies to oxidized LDL and atherosclerosis in diabetic and non-diabetic subjects" (page 742). "We found only a weak correlation between antibodies to copper-oxidized LD and antibodies to MDA-LDL in the group as a whole ..." (page 744).

170. Liu K, Cuddy TE, Pierce GN, "Oxidative status of lipoproteins in coronary disease patients," *American Heart Journal* (1992), volume 123, pages 285-290. "Oxidized low-density lipoprotein (LDL) may play an important role in atherogenesis. The oxidative status of isolated LDL and very low-density lipoprotein (VLDL) were investigated in 23 patients with proven coronary disease and in 23 healthy asymptomatic control subjects. Oxidized cholesterol (4-cholesten-3-one and 20 alpha-OH cholesterol) was identified in LDL and VLDL from both groups. The content of cholesterol and 4-cholesten-3-one in LDL from patients was significantly increased in comparison with values from the control subjects. Lipid peroxidation, as assessed by malondialdehyde (MDA) formation, was barely detectable in native LDL and VLDL from the two groups. However, after incubation with a free radical-producing system, MDA levels in LDL from patients were significantly higher than those in control subjects. Lysine reactivity in LDL after incubation with an oxidizing agent, CuSO4, was similar between groups. However, lysine reactivity to CuSO4 in VLDL from patients was less than that in control subjects. Our results suggest that LDL levels from patients with coronary disease have an elevated oxidized cholesterol content and are more susceptible to peroxidative modification. Conversely, the LDL apoprotein does not appear to have been oxidatively modified in these patients. The data are consistent with a role for oxidized LDL in coronary artery disease and indicate that the LDL lipid may be an important oxidation site." (Abstract) "Our results revealed that very low levels of MDA were present in LDL and VLDL from both coronary heart patients and healthy control subjects. The low MDA level indicates that little lipid peroxidation of circulating lipoproteins occurs in vivo." (page 288)

171. Palinski W, Horkko S, Miller E, Steinbrecher UP, Powell HC, Curtiss LK, Witztum JL, "Cloning of Monoclonal Autoantibodies to Epitopes of Oxidized Lipoproteins

from Apolipoprotein E-deficient Mice," *Journal of Clinical Investigation* (1996), volume 98, pages 800-814. "Many reactive products may be formed when LDL undergoes lipid peroxidation, which in turn can react with lipids, apoproteins, and proteins, generating immunogenic neoepitopes. Autoantibodies recognizing model epitopes of oxidized low density lipoprotein, such as malondialdehydelysine, occur in plasma and in atherosclerotic lesions of humans and animals. Because apo E-deficient mice develop particularly high titers of such autoantibodies, we used their spleens to clone 13 monoclonal antibodies to various epitopes of oxidized LDL ('E0 antibodies'). Binding and competitive RIAs demonstrated significant differences in fine specificity even between E0 antibodies initially selected for binding to the same screening antigen. For example, some E0 antibodies selected for binding to malondialdehyde-LDL also recognized copper oxidized LDL, acrolein-LDL, or LDL modified by arachidonic or linoleic acid oxidation products. Circulating IgG and IgM autoantibodies binding to copper-oxidized LDL, 4-hydroxynonenal-LDL, acrolein-LDL, and LDL modified with arachidonic or linoleic acid oxidation products were found in apo E-deficient mice, suggesting that the respective antigens are formed in vivo. Epitopes recognized by some of the E0 monoclonal antibodies were also found on human circulating LDL. Each of the E0 monoclonal antibodies immunostained rabbit and human atherosclerotic lesions, and some of them yielded distinct staining patterns in advanced lesions. Together, this suggests that the natural monoclonal antibodies recognize different epitopes of complex structures formed during oxidation of lipoproteins, or epitopes formed independently at different lesion sites. Our data demonstrate that a profound immunological response to a large number of different epitopes of oxidized lipoproteins occurs in vivo. The availability of 'natural' monoclonal autoantibodies should facilitate the identification of specific epitopes inducing this response." (Abstract)

172. Schier R, McCall A, Adams GP, Marshall KW, Merritt H, Yim M, Crawford RS, Weiner LM, Marks C, Marks JD, "Isolation of Picomolar Affinity Anti-c-erbB-2 Single-chain Fv by Molecular Evolution of the Complementary Determining Regions in the Center of the Antibody Binding Site," *Journal of Molecular Biology* (1996), volume 263, pages 551-567. "The increase in affinity, and its absolute value, are comparable to the largest values observed for antibody affinity maturation in vivo or

in vitro and indicate that mutation of V(L) and V(H) CDR3 may be a particularly efficient means to increase antibody affinity." (Abstract)

173. Winzor DJ, De Jersey J, "Biospecific Interactions: Their Quantitative Characterization And Use For Solute Purification," *Journal of Chromatography* (1989), volume 492, pages 377-430. "Biospecificity is due largely to the formation and dissociation of non-covalent complexes between small molecules and macromolecules, or between two macromolecules" (Abstract). "[T]he association constants for specific interactions between ligands and macromolecules can range from ... 10^3 to 10^{15} M^{-1} ..." (page 381).

* * *

These documents were cited by the Examiner in an August 22, 2006 Office Action in U. S. Patent Application Serial No. 10/802,643, filed March 17, 2004, which is a continuation of U. S. Patent Application Serial No. 09/446,259, filed December 20, 1999 (now U. S. Patent No. 6,727,102, which is Document 159 in the Second Supplemental Information Disclosure Statement in the above-captioned application).

Documents 169-171 are believed to be more relevant and documents 172-173 less relevant; however, independent consideration of these documents and of their relevance is respectfully requested. The Examiner is also requested to initial and return a copy of the accompanying PTO-1449 Form to evidence such consideration.

This SEVENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT is being filed in accordance with the provisions of 37 CFR § 1.97(b)(3) based on applicant's belief that it is being filed before the mailing of a first Office Action

on the merits. Thus, **a fee is not required for filing this paper**; however, if any fee is owed, please charge the fee to our Deposit Account No. 02-4467.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop Amendment, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on August 30, 2006
(Date of Deposit)

Stephen P. Gilbert
Signature

Respectfully submitted,

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Form PTO-1449 (Rev.)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: C15043/174944	APPLICATION NO.: 10/777,543
	INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	APPLICANT Harold M. Bates	
		FILING DATE February 12, 2004	GROUP: 1646

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

			Griffin ME, McInerney D, Fraser A, Johnson AH, Collins PB, Owens D, Tomkin GH. "Autoantibodies to Oxidized Low Density Lipoprotein: the Relationship to Low Density Lipoprotein Fatty Acid Composition in Diabetes." *Diabetic Medicine* (1997), volume 14, pages 741-747.
			Liu K, Cuddy TE, Pierce GN. "Oxidative status of lipoproteins in coronary disease patients." *American Heart Journal* (1992), volume 123, pages 285-290.
			Palinski W, Horkko S, Miller E, Steinbrecher UP, Powell HC, Curtiss LK, Witztum JL. "Cloning of Monoclonal Autoantibodies to Epitopes of Oxidized Lipoproteins from Apolipoprotein E-deficient Mice." *Journal of Clinical Investigation* (1996), volume 98, pages 800-814.
			Schier R, McCall A, Adams GP, Marshall KW, Merritt H, Yim M, Crawford RS, Weiner LM, Marks C, Marks JD. "Isolation of Picomolar Affinity Anti-c-erbB-2 Single-chain Fv by Molecular Evolution of the Complementary Determining Regions in the Center of the Antibody Binding Site." *Journal of Molecular Biology* (1996), volume 263, pages 551-567.
			Winzor DJ, De Jersey J. "Biospecific Interactions: Their Quantitative Characterization And Use For Solute Purification." *Journal of Chromatography* (1989), volume 492, pages 377-430.

EXAMINER	DATE CONSIDERED

Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.